

Paoloni JA, Appleyard RC, et al. Topical Nitric Oxide Application in the Treatment of Chronic Extensor Tendinosis at the Elbow. Am J Sports Med 2003;31(6):915-920.

Design: Randomized clinical trial

Population/sample size/setting:

- 86 patients (42 men, 44 women, median age 46) treated for chronic lateral epicondylitis (LE) at a university orthopedics department in Australia
- Exclusion criteria included fewer than 3 months of symptoms, current pregnancy, previous surgery, dislocation of affected elbow or wrist, distal neurological signs, or local steroid injection in previous 3 months
- Median duration of symptoms was 17 months (range, 3 to 232 months)

Main outcome measures:

- All patients received a transdermal patch to be placed daily and left in place for 24 hours; the position of the patch was to be rotated daily
- Randomization was to active glyceryl trinitrate (GTN) patch (one quarter of a 5 mg per 24 hour patch, n=43) or to a placebo patch (n=23)
- All patients had identical instruction in tendon rehabilitation (rest, graduated activity, stretching, muscle strengthening)
- Follow-up assessments were done at 2, 6, 12, and 24 weeks by a single physician examiner; patient-rated outcome information was gathered at the same intervals
- The physician examiner recorded the degree of tenderness at the elbow, a dynamometer measurement of third finger M-P extension, wrist extensor tendon mean peak force, and total work using a modified chair pick-up test
- The patient-rated outcomes were elbow pain with activity, elbow pain at night, and elbow pain at rest
- Both groups had decreasing pain with activity between baseline and 24 weeks; the GTN group had significantly greater pain relief at the 2 week mark than the placebo group, and had a trend to lower pain scores than placebo at the other follow-up visits
- Mean peak force and total work both increased at successive follow-up evaluations; the GTN group improved more than the placebo group
- Excellent patient-reported outcome were recorded at 24 weeks by 81% of the GTN group and by 60% of the placebo group (asymptomatic with activities of daily living)
- Headache occurrence was equally common in both groups (63% of GTN and 58% of placebo)
- In GTN group, 21% had a skin rash (vs. 9% of placebo); 1 GTN patient had facial flushing and cutaneous angiodyplasia
- Treatment was discontinued in 5 GTN patients and 4 placebo patients

Authors' conclusions:

- Topical GTN with tendon rehabilitation was more effective than tendon rehabilitation alone in improving symptoms and function of LE

- Tendon rehabilitation is a critically important part of the treatment regimen when GTN is administered
- There is great variation in transdermal GTN absorption across a population; optimum dosing and administration of GTN must be determined by future studies

Comments:

- The study is best seen as a pilot study; the dosing and administration are not clear (the same authors published a dose-finding follow-up study in 2009)
- Exclusion criteria are given, but the inclusion criteria are sparse (over age 18 is the only criterion reported)
- Because the distribution of the data did not allow confidence intervals to be calculated (nonparametric testing was used), the amount of uncertainty in the data could not be quantified
- The authors did report an “effect size” which assumed a parametric distribution of data (a z score), and their reported effect size should be disregarded
- The distribution of the duration of symptoms should have been more completely reported; one patient had been symptomatic for 232 months—almost 20 years, and the duration of symptoms might alter the response to GTN
- Baseline data was not reported in a tabular form, making it difficult to compare the treatment groups
- If GTN is recommended in the guideline, it will be an off-label use (angina is still the only FDA approved use)
- Exclusion criteria did not include use of nitrates or sildenafil, although the authors do recognize the need for caution if these agents are used by the patient

Assessment: Inadequate for an evidence statement (more information is needed about the inclusion characteristics of the enrolled patients; the dose of GTN cannot be taken from this study)